Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SYSTEMATIC REVIEWS AND META-ANALYSES

Hypertension is a clinically important risk factor for critical illness and mortality in COVID-19: A meta-analysis

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Meta-analysis

Abstract *Aims:* As reported, hypertension may play an important role in adverse outcomes of coronavirus disease-2019 (COVID-19), but it still had many confounding factors. The aim of this study was to explore whether hypertension is an independent risk factor for critical COVID-19 and mortality.
Data synthesis: The Medline, PubMed, Embase, and Web of Science databases were systematically searched until November 2020. Combined odds ratios (ORs) with their 95% confidence interval (CIs) were calculated by using random-effect models, and the effect of covariates was analyzed using the subgroup analysis and meta-regression analysis. A total of 24 observational studies with 99,918 COVID-19 patients were included in the meta-analysis. The proportions of hypertension in critical COVID-19 were 37% (95% CI: 0.27 −0.47) when compared with 18% (95% CI: 0.14 −0.23) of noncritical COVID-19 patients, in those who died were 46% (95%CI: 0.37 −0.55) when compared with 22% (95% CI: 0.16 −0.28) of survivors. Pooled results based on the adjusted OR showed that patients with hypertension had a 1.82-fold higher risk for critical COVID-19 (aOR: 1.82; 95% CI: 1.19 − 2.77; $P = 0.005$) and a 2.17-fold higher risk for COVID-19 mortality (aOR: 2.17; 95% CI: 1.67 − 2.82; $P < 0.001$). Subgroup analysis results showed that male patients had a higher risk of developing to the critical condition than female patients (OR: 3.04; 95%CI: 2.06 − 4.49; $P < 0.001$) and age >60 years was associated with a significantly increased risk of COVID-19 mortality (OR: 3.12; 95% CI: 1.93 − 5.05; $P < 0.001$). Meta-regression analysis results also showed that age (Coef. $= 2.3\times10^{-2}$, $P = 0.048$) had a significant influence on the association between hypertension and COVID-19 mortality.
Conclusions: Evidence from this meta-analysis suggested that hypertension was independently associated with a significantly increased risk of critical COVID-19 and inhospital mortality of COVID-19.

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic presents an unprecedented health crisis to the entire world. As of August 30, the disease has spread to more than 200 countries and territories, including the USA, India, Brazil, and Spain; almost 24 million people have been diagnosed with COVID-19 and approximately 836,570 deaths all over the world according to the report of the World Health Organization (WHO)[1,2]. Therefore, understanding the risk factors associated with COVID-19 susceptibility and severity is crucial to disease control.

Previous studies have shown that common comorbidities (diabetes or cardiovascular, respiratory, or kidney disease) were significantly associated with the increased risk of adverse outcomes in patients with COVID-19 [3–6]. Increasing numbers of reports have also linked hypertension to critical COVID-19 and death. Wang et al. [7] reported on 138 COVID-19 patients hospitalized in Wuhan, China: 31% had hypertension. Of those requiring intensive care unit (ICU) admission, 58% had hypertension when compared with 22% who did not. Zhou et al. [8] reported on 191 hospitalized patients from Wuhan: 30% had hypertension, with 48% of those who died having hypertension when compared with 23% of survivors. However, Yang et al. [9] and Huang et al. [10] reported that hypertension was not more common in those in China with COVID-19 than the general population. Therefore, great differences were shown in the current studies. In addition, the small sample size of patients in these studies further limits its applicability. More importantly, most conclusions were obtained from univariate estimates only. Several studies have shown that the pooled effects based on the adjusted effect estimates were significantly reduced or even disappeared [11–13]. Therefore, whether hypertension is an independent risk factor for COVID-19 patients is unclear.

Therefore, it is urgently required to clarify the association between hypertension and the adverse outcomes of COVID-19 patients. Compared with the previously published meta-analyses, we herein performed a subgroup analysis based on the adjusted effect estimates to explore whether hypertension is an independent risk factor for critical COVID-19 and mortality. In addition, age, sex, and some comorbidities were analyzed by meta-regression analyses.

Methods

This meta-analysis was planned and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [14]. We also followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [15].

Literature search strategy

A systematic search of published articles was conducted in the Medline, PubMed, Embase, Web of Science, and Cochrane Library databases up to November 17, 2020. Following search terms are used: ("coronavirus disease 2019" OR "COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "nCoV-2019") AND ("hypertension" OR "risk factor" OR "characteristics" OR "clinical features") AND ("clinical trial" OR "observational study" OR "cohort" OR "trial" OR "case–control" OR "study"). We also reviewed the reference lists from the retrieved articles and manual search to identify additional relevant studies that may not have been identified by our database searches.

Inclusion and exclusion criteria

Studies that met the following criteria were included in this meta-analysis: 1) observational studies in humans with either cohort or case–control or cross-sectional design; 2) concerning the effects of hypertension on COVID-19; 3) patient was diagnosed as COVID-19 by the laboratory test and age $\geqslant$18 years old; 4) outcomes of COVID-19 infection severity reported; 5) provided data of death, critical or noncritical in patients with hypertension; and 6) publication in English. The exclusion criteria were the following: 1) duplicate studies (including duplicate patients data); 2) reviews, reports, conferences, and commentaries; 3) insufficient data; and 4) sample size $<$10. In this study, patients with acute respiratory distress syndrome who require life support, mechanical ventilation, or ICU support are considered as critical illness patients. The diagnosis of hypertension was given by the patient's physician prior to the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These data were collected from patients' documented medical files (e.g., the diagnosed patients with antihypertensive drugs or with a history of hypertension). Two of the authors independently searched all references and any discrepancies were resolved by all authors.

Data extraction

Two authors (Yanbin Du and Nan Zhou) performed data extraction, again any disagreements were discussed and resolved by consensus. For each study, the following information was collected: first author's name, publication year, country, study design, age and sex distribution, sample size, multivariate-adjusted OR with corresponding 95% CI as well as adjusted factors, number of patients with hypertension in critical and noncritical COVID-19 group, number of patients with hypertension in the survivors and nonsurvivors group.

Quality assessment

Quality assessment of eligible studies was performed by two investigators (Wenting Zha and Yuan LV), by using the Newcastle–Ottawa Quality Assessment Scale (NOS) [16]. Each study was assessed on the basis of three broad perspectives: selection (0–4 points), comparability (0–2 points), and exposure (0–3 points) with a score ranging from 0 to 9 points. We assigned scores of 0–3, 4–6, and

7–9 points for low, moderate, and high quality of the studies, respectively.

Statistical analysis

The odds ratio (OR) and 95% confidence intervals (CI) were considered as the common measurement of the association between hypertension and the risk of critical COVID-19 and mortality. Heterogeneity among the studies was estimated using the Q and I^2 statistic. For the Q statistics, $P < 0.10$ indicated statistically significant heterogeneity. In addition, the I^2 values of 25%, 25%–50%, 50%–75%, and >75% were classified as indicating no, small, moderate, and significant heterogeneity, respectively. Pooled ORs were obtained using a fixed-effects model, if $I^2 < 50\%$; otherwise, a random-effects model was used [17]. In addition, we performed a subgroup analysis using geography (China vs. non-China), age (≤60 years vs. >60 years), sex (the percentage of men > 60% vs. the percentage of men ≤60%), sample size (≤1000 vs. > 1000), and multivariate analysis (Yes vs. No) to explore the effects of covariates. We also performed meta-regression analyses to examine the effect of age, sex, and comorbidities (diabetes and cardiovascular diseases) on the association between hypertension and both critical COVID-19 and mortality.

To assess the potential publication bias, we used funnel plots and Egger's linear regression test [18]. Sensitivity analyses were carried out by excluding each study and reanalyzing the data. All statistical analyses were performed with STATA 15.1 (Stata Corp, Texas, USA). Significance was set at a $P < 0.05$, and all statistical tests were two-sided.

Results

Literature search

An electronic literature search identified 2380 studies concerning the effects of hypertension on COVID-19 patients, 2359 studies of which were excluded based on the series of reasons (first, 329 duplicated articles were excluded, then 2051 articles were screened by title and abstract, leading to the exclusion of 805 irrelevant studies and 1164 reports, reviews or meta-analysis, or letters. Finally, leaving 82 articles for full-text review, where 45 articles do not provide available data index (severity or mortality), 13 articles do not define the critical COVID-19), resulting in a total of 24 studies were included in the meta-analysis. The details of literature search are shown in Fig. 1.

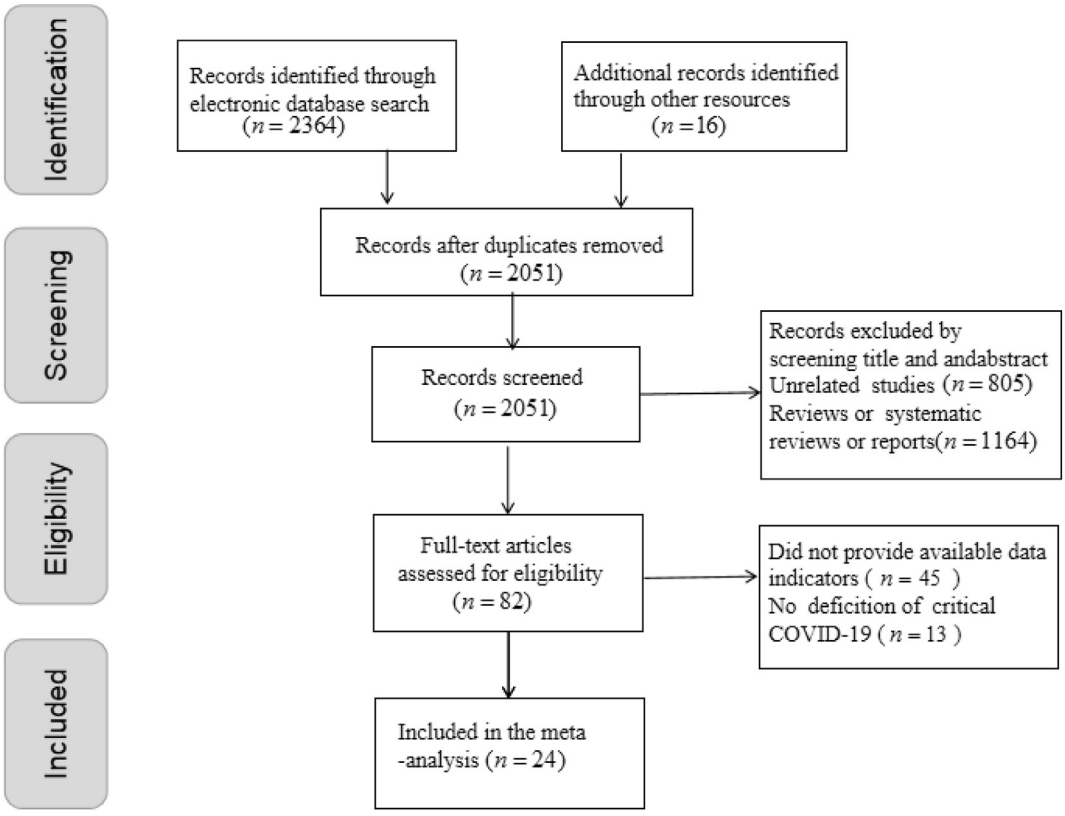

Figure 1 Flowchart of study procedure.

Study characteristics and quality assessment

The characteristics of included studies are shown in Tables 1 and 2. A total of 24 observational studies that met the inclusion criteria for our meta-analysis were published in 2020. Thirteen studies (5 reported adjusted OR [10,20,25,27,28]) explored the association between hypertension and critical COVID-19 and 12 studies (9 reported adjusted OR [8,13,30,31,33,34,36,37]) explored the association between hypertension and COVID-19 mortality. Of these studies, except two were in USA [20,30], one in Mexico [25], one in Israel [26], and others all in China. In total, 99,918 COVID-19 patients were included in this meta-analysis, including critical (n = 12,522), noncritical (n = 80,174), death (n = 1697), and survivors (n = 5525). Mean ages of patients ranged from 40 to 69 years. Sample size ranged from 27 to 89,756, the proportion of men ranged from 45% to 85%. The NOS scores of all studies ranged from 4 to 9 points, and 17 studies had a score of ≥6 points.

The percentage of hypertension in COVID-19 patients

The random-effects meta-analysis revealed that the percentage of hypertension in critical COVID-19 patients is 37% (95% CI: 0.27 −0.47 and $P < 0.001$) when compared with 18% (95% CI: 0.14 −0.23 and $P < 0.001$) in noncritical COVID-19 patients. In addition, the percentage of hypertension in nonsurvivors is 46% (95% CI: 0.37 −0.55 and $P < 0.001$) when compared with 22% (95% CI: 0.16 −0.28 and $P < 0.001$) in survivors (Supplementary materials, Figs. 1–4).

Effect of hypertension on critical COVID-19 patients

The effect of hypertension on critical COVID-19 patients was explored in 13 studies (critical = 12,522 and noncritical = 80,174). Heterogeneity test results found moderate heterogeneity in these studies (Q = 26.16, P = 0.01, and I^2 = 54.1%). In addition, a random-effects model was applied, the summary OR for 13 studies showed that COVID-19 patients with hypertension were associated with a significantly increased risk (OR: 2.92; 95% CI: 2.26 – 3.77; and $P < 0.001$) of developing the critical illness. In addition, pooled results based on the adjusted OR showed that hypertension is an independent risk factor for critical COVID-19 (aOR: 1.82; 95% CI: 1.19 – 2.77; and $P = 0.005$) (Fig. 2).

Subgroup analyses indicated that geography, ages, and sample sizes had no significant difference in the effect of

Table 1 Characteristics of patients included in the severity analysis studies.

Author and Publication Year	Country (city)	Study Design	Age (years)	Men (%)	Sample size	Critical patients		non-Critical patients		Multivariate analysis[a]
						N (%)	Hypertension (%)	M(%)	Hypertension (%)	
Lv et al., 2020 [19]	China, Wuhan	Cohort	62 (23–90)	49.44%	354	155 (43.8%)	33 (21.29%)	199 (56.2%)	23 (11.6%)	No
Wang et al., 2020 [7]	China, Wuhan	Cohort	56 (42–68)	54.3%	138	36 (26.1%)	21 (58.3%)	102 (73.9%)	22 (21.6%)	No
Kalligeros et al., 2020 [20]	USA, Rhode Island	Cohort	60 (50–72)	61.1%	103	44 (42.7%)	31 (70.4%)	59 (57.3%)	35 (59.3%)	Yes
Chen et al. 2020 [21]	China, Zhejiang	Cohort	45.3 ± 13.6	53.5%	145	43 (29.6%)	9 (20.9%)	102 (70.4%)	13 (12.7%)	No
Huang et al. 2020 [10]	China, Wuhan	Cohort	49 (41–58)	85%	41	13 (31.7%)	2 (15%)	28 (68.3%)	4 (14%)	Yes
Qin et al. 2020 [22]	China, Wuhan	Cohort	58 (22–95)	52%	452	286 (63.3%)	105 (36.7%)	166 (36.7%)	30 (18.1%)	No
Shi et al. 2020 [23]	China, Wuhan	Cohort	46 ± 17	53.2%	487	49 (10.1%)	26 (53.1%)	438 (89.9%)	73 (16.7%)	No
Xu et al., 2020 [24]	China	Cohort	60.5 ± 17.2	69%	703	55 (7.8%)	30 (54.5%)	648 (92.2%)	89 (13.7)	No
Giannouchos et al., 2020 [25]	Mexico	Cohort	44 (18–65)	67%	89,756	11,706 (13%)	4740 (40.5%)	78,050 (87%)	14,049 (18%)	Yes
Edward et al. 2020 [26]	Israel	Cohort	52 ± 20	65%	162	26 (16%)	13 (50%)	136 (84%)	36 (26.5%)	No
Liu et al. 2020 [27]	China, Wuhan	Cohort	66 (51–70)	63.6%	78	11 (14.1%)	2 (18.2%)	67 (85.9%)	6 (9%)	Yes
Wan et al. 2020 [28]	China, Chongqing	Cohort	56 (52–73)	52.5%	135	40 (29.6)	4 (10%)	95 (70.4%)	9 (9.4%)	Yes
Zhang et al. 2020 [29]	China, Wuhan	Cohort	57 (25–87)	56.9%	140	58 (41.4%)	22 (37.9%)	82 (58.6%)	20 (24.4%)	No

N: The total number of critical patients; M: The total number of non-critical patients.
[a] The multivariate analysis was adjusted for age, sex, history of cancer, smoking, diabetes cardiovascular diseases, body mass index (BMI), chronic kidney disease (CKD), and other chronic diseases.

Table 2 Characteristics of patients included in the mortality analysis studies.

Author and Publication Year	Country (city)	Study Design	Age (years)	Men (%)	Sample size	non-Survivors		Survivors		Multivariate analysis[a]
						N (%)	Hypertension (%)	M(%)	Hypertension (%)	
Klang et al., 2020 [30]	USA, New York	Cohort	40 (34–46)	69.4%	572	60 (10.5%)	10 (16.7%)	512 (89.5%)	25 (4.9%)	Yes
Klang et al., 2020 [30]	USA, New York	Cohort	68 (60–77)	54%	2834	1076 (38.0%)	502 (46.7%)	1758 (62%)	404 (22.9%)	Yes
Zhou et al.,2020 [8]	China, Wuhan	Cohort	56 (46–67)	62%	191	54 (28.3%)	26 (48%)	137 (71.7%)	32 (23%)	Yes
Huang et al.,2020 [31]	China, Wuhan	Cohort	62 (40–70)	54.3%	310	113 (36.5%)	28 (24.8%)	197 (63.5%)	30 (15.2%)	Yes
Yuan et al., 2020 [32]	China, Wuhan	Cohort	60 (47–69)	45%	27	10 (37%)	5 (50%)	17 (63%)	0 (0%)	No
Xu et al.,2020 [26]	China	Cohort	64.7 ± 13.4	73%	703	33 (6.3%)	17 (51.5%)	659 (93.7%)	93 (14.1%)	No
Fu et al.,2020 [33]	China, Wuhan	Case-cohort	55 (40–75)	49.3%	200	34 (17%)	22 (64.7%)	166 (83%)	79 (47.6%)	Yes
Sun et al., 2020 [34]	China, Wuhan	Cohort	72 (66–78)	67.8%	244	121 (49.6%)	76 (63.3%)	123 (50.4%)	42 (34.1%)	Yes
Du et al., 2020 [35]	China, Wuhan	Cohort	57.6 ± 13.7	54.2%	179	21 (11.7%)	13 (61.9%)	158 (88.3%)	45 (28.5%)	No
Shi et al. 2020 [36]	China, Wuhan	Cohort	63 (50–72)	56.5%	671	62 (9.2%)	37 (59.7%)	609 (81.8%)	162 (26.6%)	Yes
Li et al. 2020 [37]	China, Wuhan	Cross-sectional	68 (58–79)	67.5%	1004	40 (4%)	20 (50%)	964 (96%)	215 (22.3%)	Yes
Wang et al. 2020 [13]	China, Wuhan	Cohort	51 (36–65)	57%	107	19 (17.8%)	4 (21%)	88 (82.2%)	9 (10.2%)	Yes

N: The total number of non-survivors; M: The total number of survivors.
[a] The multivariate analysis was adjusted for age, sex, history of cancer, smoking, diabetes cardiovascular diseases, body mass index (BMI), chronic kidney disease (CKD), and other chronic diseases.

hypertension on critical COVID-19. However, male patients had a slightly higher risk of critical COVID-19 than female patients (the percentage of men > 60%; OR: 3.04; 95% CI: 2.06 – 4.49; the percentage of men ≤ 60%: OR: 2.68; and 95% CI: 1.72 – 4.17) (Table 3). Meta-regression analysis results showed that age ($P = 0.87$) and sex ($P = 0.74$) had no significant influence on the association between hypertension and critical COVID-19 (Fig. 4). In addition, some comorbidities (diabetes: $P = 0.46$, cardiovascular diseases: $P = 0.52$) did not appear to exert a significant effect on the association between hypertension and critical COVID-19.

Effect of hypertension on COVID-19 mortality

The effect of hypertension on COVID-19 mortality was explored in 12 studies (death = 1687 and survivors = 5525). Combined results through the random-effects model revealed that hypertension significantly increased COVID-19 mortality (OR: 2.59; 95% CI: 1.91–3.51; and $P < 0.001$) with moderate heterogeneity in these studies (Q = 33.59, P < 0.001, and $I^2 = 67.3\%$). Pooled results based on the adjusted OR showed that hypertension was an independent risk factor for COVID-19 mortality (aOR: 2.17; 95% CI: 1.67 – 2.82; and $P < 0.001$) (Fig. 3).

Subgroup analyses indicated that patients with hypertension and age >60 years (OR: 3.12 and 95% CI: 1.93 – 5.05) had a significantly higher COVID-19 mortality than age <60 years (OR: 2.06 and 95% CI: 1.56–2.73) (Table 3). Meta-regression analysis results also showed a significant influence of increasing age on the association between hypertension and mortality of COVID-19 (Coef. = 2.3×10^{-2}; $P = 0.048$). However, sex ($P = 0.89$), diabetes ($P = 0.354$), and cardiovascular diseases ($P = 0.145$) did not exert a significant effect on the association between hypertension and COVID-19 mortality.

Sensitivity analysis and publication bias

Sensitivity analysis results showed that removing each study did not significantly alter the overall effect of hypertension on critical COVID-19 (OR altered between 1.79 and 4.23) and COVID-19 mortality (OR altered between 1.77 and 3.87) (Supplementary materials, Figs. 5–6).

No publication bias was detected in the current meta-analysis, although slight asymmetries were observed in the funnel plots (Fig. 5); Egger's linear regression test was not statistically significant (severity: $P = 0.164$ and mortality: $P = 0.191$).

Discussion

Coronavirus is an enveloped, nonsegmented, single-stranded RNA virus. At present, six human coronaviruses

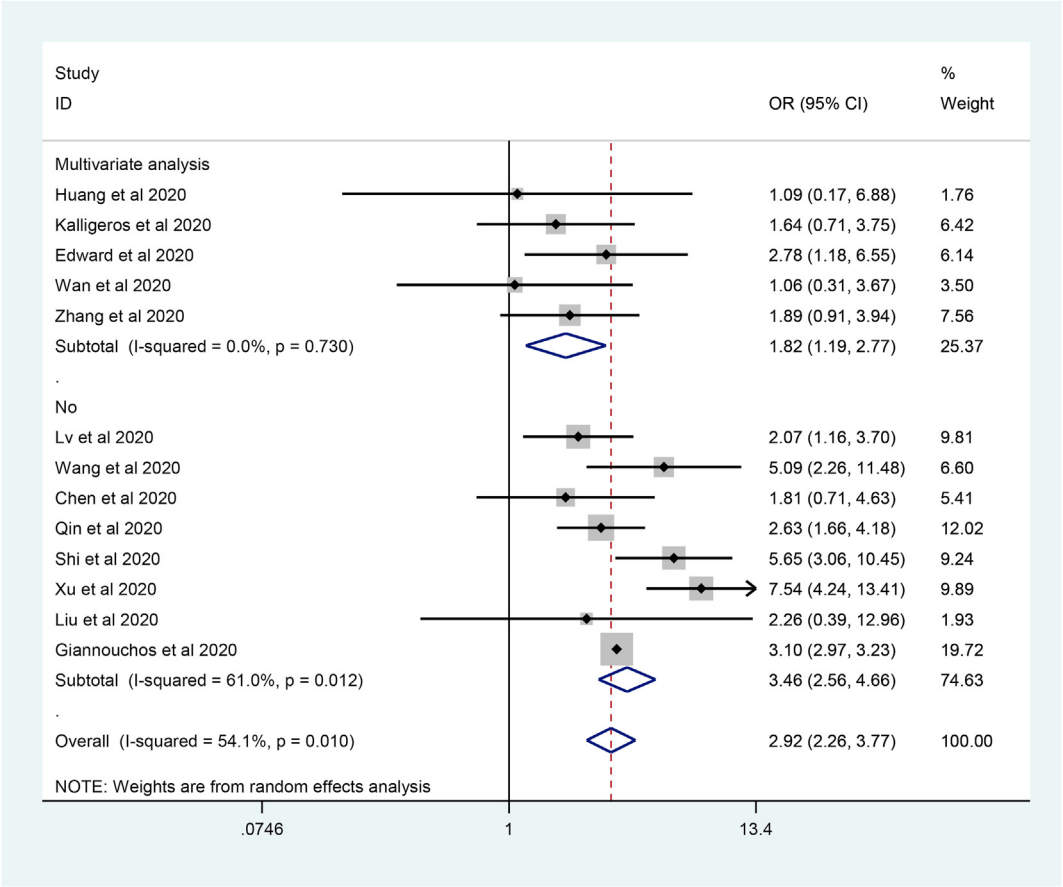

Figure 2 Effects of hypertension on critical COVID-19 patients.

have been identified [38]. Moreover, the SARS-CoV-2, which isolated from the lower respiratory tract of pneumonia patients with unknown causes, is identified as the seventh human coronaviruses.

According to previous research on SARS-CoV-2, the presence of comorbidities increased the mortality risk, with cardiovascular diseases and diabetes being the most important components [39]. Hypertension is the leading risk factor for premature death and disability worldwide, 31.2% of adults were estimated to have hypertension worldwide [40]. Therefore, considering the virtually unstoppable current trajectory of SARS-CoV-2, together with the high prevalence of hypertension, we carried out this meta-analysis to explore the effect of hypertension on COVID-19 patients. The results revealed that COVID-19 patients with hypertension were associated with a significantly increased 2.6-fold risk of developing into the critical or mortal condition. Comparing the general population, the incidence of hypertension in the critical COVID-19 group (37%) and death group (46%) are obviously much higher. However, we did not find that people with hypertension are more susceptible to 2019-nCoV infection. The prevalence of hypertension (21.53%) in people infected with the virus is about the same as in the general population, even slightly lower.

To eliminate the effect of confounding factors on the association between hypertension and COVID-19. We conducted a meta-analysis based on the adjusted OR, although pooled ORs were significantly reduced in the multivariate analysis (aOR: 1.82; 95% CI: 1.19 – 2.77) when compared with that in the univariate analysis (OR:3.46 and 95% CI: 2.56–4.66), the results also showed that hypertension was an independent risk factor for critical COVID-19. Similarly, the results showed that hypertension was an independent risk factor for COVID-19 mortality (multivariate analysis: aOR, 2.17 and 95% CI, 1.67 – 2.82; univariate analysis: OR, 5.82 and 95% CI, 3.34 – 10.14). Meta-regression analysis results also showed that diabetes and cardiovascular diseases did not exert a significant effect on the association between hypertension and COVID-19.

Our study found that male patients (66.2%) are more susceptible to develop into the critical or mortal condition than female patients (33.8%), possibly because of the protection of X chromosome and sex hormones, which play an important role in innate and adaptive immunity [41]. At the same time, men tend to be associated with bad lifestyle habits such as smoking and underlying diseases, which are reported to be associated with an increased risk of critical COVID-19 [42,43]. In addition, the subgroup analysis and meta-regression analysis results indicated that age had a significant effect on the association between hypertension and mortality of COVID-19 patients. Older patients (age >60 years) with hypertension had a 3.12-fold

Table 3 Subgroups analysis of association between hypertension and Critical COVID-19 and mortality.

COVID-19	Subgroups	Study number	OR (95%CI)	Heterogeneity test		
				Q	P-value	I^2 (%)
Severity	Overall	13	2.92 (2.26–3.77)	26.16	<0.001	54.1%
	Geography					
	China	10	2.91 (1.94–4.38)	23.98	0.004	62.3%
	Non-china	3	2.94 (2.34–3.70)	2.34	0.311	14.4%
	Age					
	≤60 years	10	2.92 (2.26–3.75)	12.74	0.12	37.2%
	>60 years	3	2.90 (1.25–6.74)	13.51	0.004	73.1%
	The percentage of men					
	≤60%	6	2.68 (1.72–4.17)	12.45	0.053	51.8%
	>60%	7	3.04 (2.06–4.49)	13.47	0.0019	62.9%
	Sample size					
	≤1000	11	2.78 (1.95–3.97)	31.21	0.001	58.1%
	>1000	2	3.1 (2.97–3.23)	4.51	0.034	77.8%
	Multivariate analysis					
	Yes	5	1.82 (1.19–2.77)	2.03	0.73	0
	No	8	3.46 (2.57–4.67)	17.94	0.012	61%
Mortality	Overall	12	2.59 (1.91–3.51)	33.59	<0.001	67.3%
	Age					
	≤60 years	5	2.06 (1.56–2.73)	4.89	0.429	0
	>60 years	7	3.12 (1.93–5.05)	30.17	0.021	59.8%
	The percentage of men					
	≤60%	7	2.49 (1.64–3.79)	10.11	0.072	50.5%
	>60%	5	2.76 (1.82–4.18)	17.10	0.009	64.9%
	Multivariate analysis					
	Yes	9	2.17 (1.67–2.82)	17.09	0.029	53.2%
	No	3	5.82 (3.34–10.14)	1.41	0.494	0

Abbreviations: OR (95%CI): odds ratio and 95% confidence intervals.

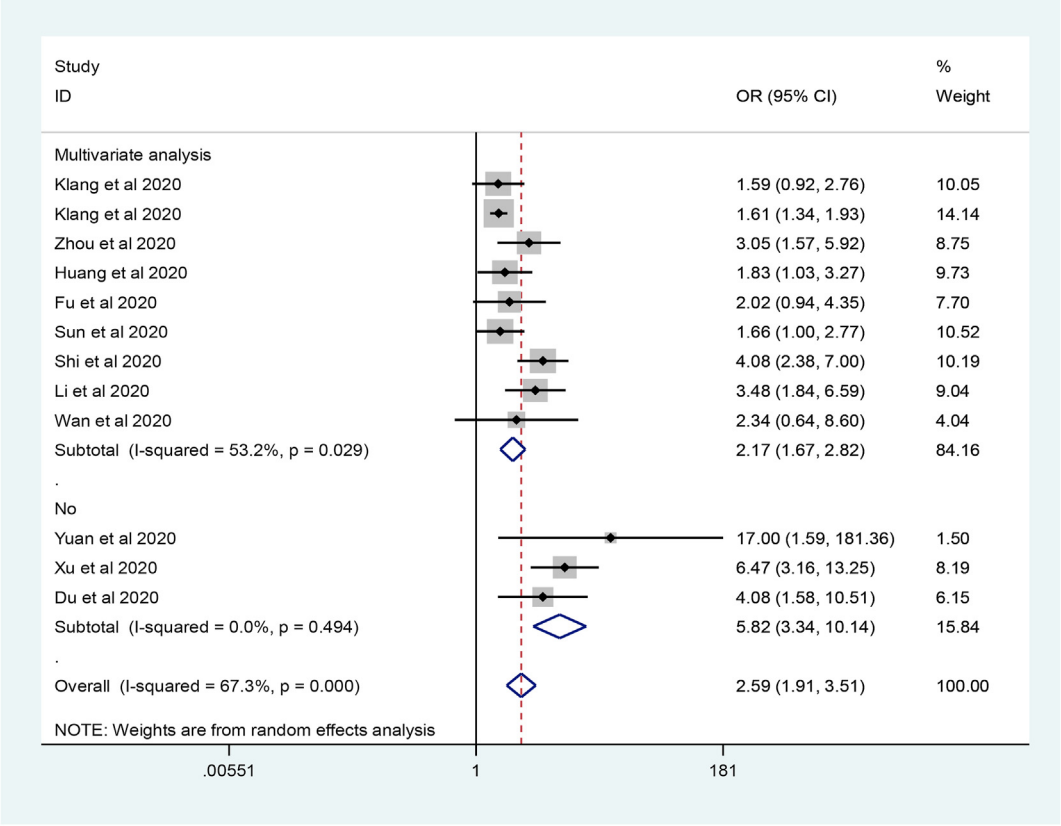

Figure 3 Effects of hypertension on COVID-19 mortality.

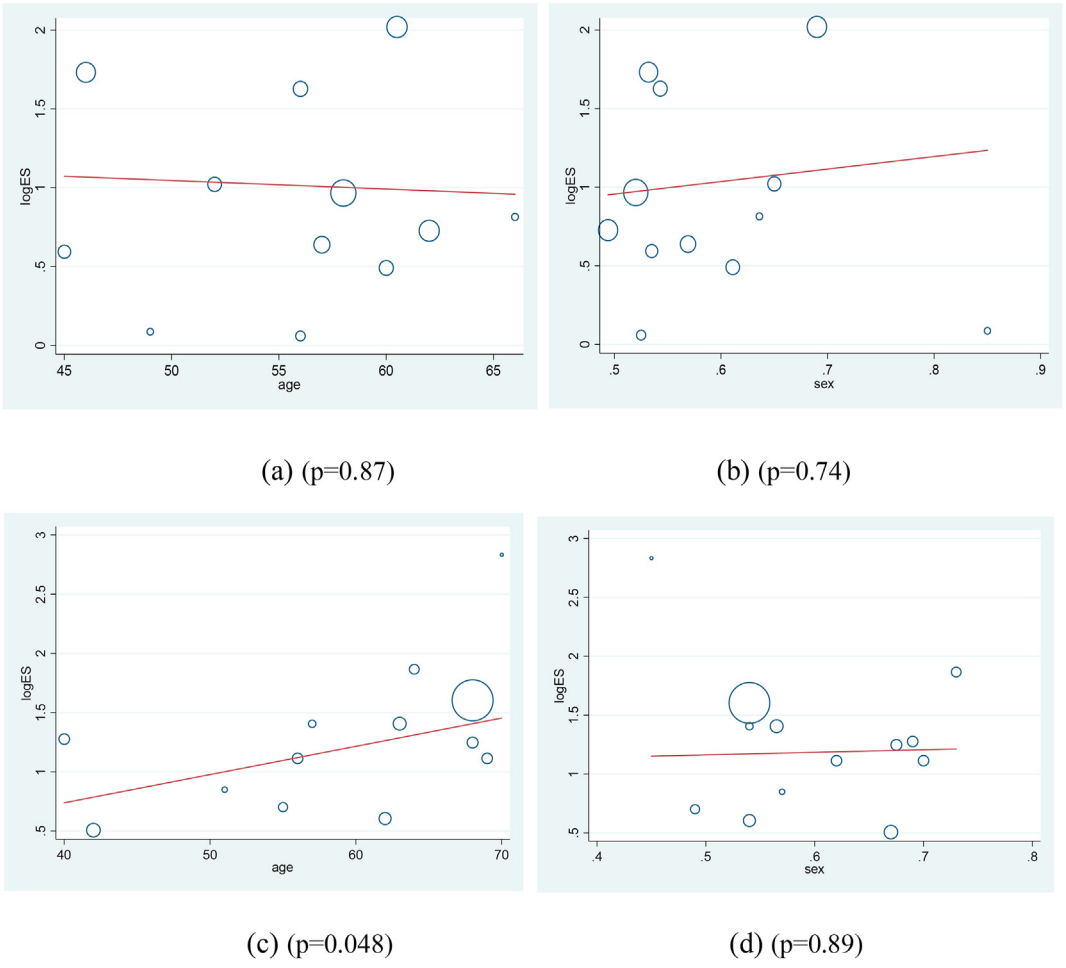

Figure 4 Random-effects meta-regression analysis of the effect of age and sex on association between hypertension and critical COVID-19 (a,b) and mortality (c,d).

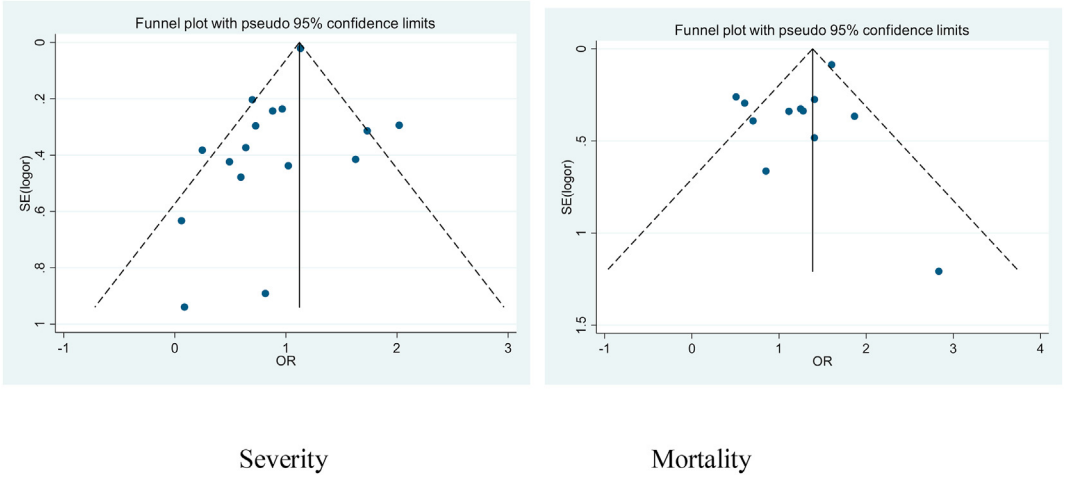

Figure 5 Funnel plots of detecting publication bias in the studies reporting the effects of hypertension on critical COVID-19 and mortality.

higher risk of COVID-19 death. This may be because the elderly weight and muscle mass start to decline, and cause immune senescence. In addition, older people are more prone to develop diabetes, hypertension, and cardiovascular diseases, which are reported to be associated with an increased risk of critical COVID-19.

Our study also found that COVID-19 patients with hypertension in other countries had a higher risk of developing into the critical or mortal condition than in China. There may be two reasons: (1) The prevalence of hypertension in China (23.2%) [44] is lower than the worldwide level (31.2%) [40]. (2) China has taken effective measures to control and treat COVID-19, avoiding disease progression. For example, isolating the infected patients and close contacts, wearing masks when traveling.

The underlying mechanism of effect of hypertension on COVID-19 is unclear now, but several mechanisms have been discussed. SARS-CoV-2 attacks the alveolar epithelial cells through angiotensin-converting enzyme 2 (ACE2) [45]. Some interesting studies have shown that the administration of some antihypertensive drugs such as ACE inhibitors (ACEis) [46] and angiotensin receptor blockers [47] may be associated with enhanced ACE2 expression at the cell surface, thus ultimately supplying SARS-CoV-2 with a larger number of "anchors" for infecting cells. However, it cannot be excluded that hypertensive patients undergoing renin-angiotensin-aldosterone system inhibition, particularly those taking ACEis, may be more susceptible to SARS-CoV-2 infection, which would ultimately translate into a higher risk of developing into adverse COVID-19 consequences [48]. On the other hand, others have argued that hypertensives may experience a decreased ACE2 expression, which when bound by SARS-CoV-2 attenuates residual ACE2, leading to elevated angiotensin II levels driving the development of COVID-19 [49]. Moreover, evidence convincingly attest that both pulmonary and systemic hypertension are risk factors for unfavorable progression in patients with pneumonia [50]. Therefore, it is plausible that the coexistence of hypertension and SARS-CoV-2 infection would interplay to synergistically increase the risk of unfavorable prognosis as compared to normotensive COVID-19 patients.

This meta-analysis has several obvious strengths. First, this is the latest study that comprehensively assessed the effect of hypertension on COVID-19 patients, and the results confirmed that hypertension is an independent risk factor for critical COVID-19 and mortality. Secondly, our findings depended on a much larger sample size involving a total of 99,918 individuals from all over the world. Third, we performed a multivariate subgroup and meta-regression analyses to fully explore the potential effect of confounding factors on associations between hypertension and COVID-19.

Meanwhile, several potential limitations of our study deserve mention. First, the included studies reported the adjusted effect estimates, but the factors adjusted in each study were not entirely consistent. Secondly, the stage of hypertension and whether it is controlled or poorly controlled are unknown. Third, the majority of patients included in the meta-analysis were of China, and it was not possible to test for ethnic-specific differences in the risk of critical COVID-19 and COVID-19 linked death, because of the limited studies in non-China individuals. Therefore, further studies, particularly in Europe and America populations, are needed to confirm these findings, and future mechanistic studies are also required to better understand the link between hypertension and the risk of severe disease and inhospital mortality associated with COVID-19.

Conclusions

In conclusion, results from this meta-analysis indicate that hypertension is a clinically important risk factor for the adverse outcomes of patients with COVID-19. Therefore, COVID-19 patients with hypertension should be paid more attention to in hospitals, particularly those male patients or those older than 60 years. In addition, our findings also highlighted that more, not less, must be done to tackle and prevent hypertension in our societies for the prevention of chronic disease and greater adverse reactions to viral pandemics.

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Author contributions

Yanbin Du conceived the idea, performed the statistical analysis, and drafted this meta-analysis. Wenting Zha and Nan Zhou conducted the systematic search, screened the articles, and extracted the data. Yuan Lv and Wenting Zha are the guarantors of the overall content. All authors revised and approved the final manuscript.

Ethics of human subject participation

Not applicable.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.12.009.

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